Translational Highlights in Breast and Ovarian Cancer 2019 - Immunotherapy, DNA Repair, PI3K Inhibition and CDK4/6 Therapy

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Thieme

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Translationale Highlights Mamma- und Ovarialkarzinom 2019 – Immuntherapien, DNA-Reparatur, PI3K-Inhibition und CDK4/6-Therapien

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ABSTRACT

In the near future, important translational questions of clinical relevance will be adressed by studies currently in progress. On the one hand, the role of PD-L1 expression must be further understood, after it was found to be relevant in the use of atezolizumab in first-line therapy of patients with metastatic triple-negative breast cancer (TNBC). No association between efficacy and PD-L1 expression was found in a neoadjuvant study that included pembrolizumab in TNBC. The pathological complete response rate (pCR) was higher in both patient groups with and without PD-L1 expression when pembrolizumab was added to chemotherapy. Another future question is the identification of further patient groups in which efficacy of PARP inhibitors is seen, which are licensed for the *pBRCA1/2* germline mutation. These include, for example, patients with mutations in other genes, which are involved in homologous recombination, or patients with tumours that show an abnormality in global tests of homologous recombination deficiencies (HRD tests). The question of whether a PARP inhibitor can be given and with which chemotherapy combination partners is currently being investigated in both breast and ovarian cancer. While the data on improved overall survival are being consolidated for the CDK4/6 inhibitors, knowledge of molecular changes during the therapy and during progression on the therapy is growing. Both the accumulation of PI3K mutations and also PTEN changes might play a part in planning subsequent therapies. This review article summarises these recent developments in breast cancer and in part also in ovarian cancer.

ZUSAMMENFASSUNG

Im Rahmen von aktuell laufenden Studien werden in naher Zukunft wichtige translationale Fragestellungen von klinischer Relevanz geklärt werden. Zum einen muss die Rolle der PD-L1-Expression, nachdem sie für die Indikationsstellung für Atezolizumab in der 1. Therapielinie bei Patientinnen mit einem metastasierten triple-negativen Mammakarzinom (TNBC) von Relevanz ist, weiter geklärt werden. In einer neoadjuvanten Studie beim TNBC mit Pembrolizumab konnte kein Zusammenhang zwischen Wirksamkeit und PD-L1-Expression gefunden werden. Sowohl mit als auch ohne Expression war die pCR höher, wenn Pembrolizumab zur Chemotherapie hinzugefügt wurde. Des Weiteren wird für die bei Keimbahnmutation von *BRCA1/2* zugelassenen PARP-Inhibitoren nach weiteren Patientengruppen gesucht, in denen eine Wirksamkeit besteht. Dieses sind z. B. Patientinnen mit Mutationen in anderen Genen, die an der homologen Rekombination beteiligt sind, oder Patientinnen mit Tumoren, die bei globalen Tests zu homologen Rekombinationsdefizienzen (HRD-Tests) eine Auffälligkeit zeigen. Auch die Frage, ob und mit welchen Chemotherapie-Kombinationspartnern eine PARP-Inhibition zusammen gegeben werden kann, wird aktuell sowohl beim Mamma- als auch beim Ovarialkarzinom untersucht. Während sich die Daten zum verbesserten Gesamtüberleben bei den CDK4/6-Inhibitoren konsolidieren, wächst auch das Wissen um molekulare Veränderungen unter der Therapie und bei der Progression unter der Therapie. Sowohl die Anhäufung von PI3K-Mutationen als auch PTEN-Veränderungen könnten bei der Planung von Folgetherapien eine Rolle spielen. Diese Übersichtsarbeit fasst diese aktuellen Entwicklungen beim Mammakarzinom und teilweise auch beim Ovarialkarzinom zusammen.

Introduction

Long after the introduction of anti-hormone therapy and anti-HER2 therapy, treatments have again been introduced with the new targeted and immuno-oncological therapies (CDK4/6 inhibitors; PI3K inhibition; anti-PD-1/PD-L1 antibodies; PARP inhibitors) that are linked to a biomarker that predicts treatment efficacy. Also, the first applications from the field of machine learning have been reported, which might be of significance in this context. This review article summarises the latest information published in the last few months or presented at large international conferences like ESMO 2019.

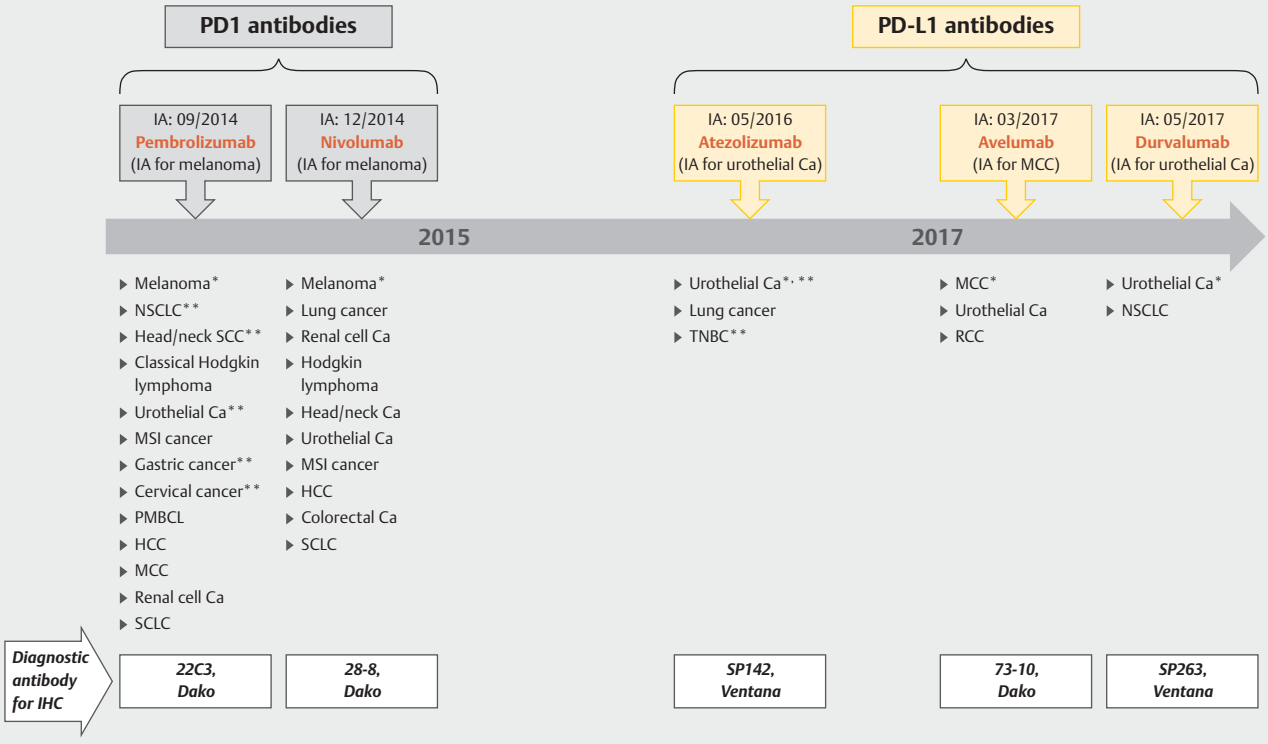
Immunotherapy

Overview

Immunotherapy with checkpoint inhibitors is becoming increasingly important in oncology. For breast cancer, PD-1 and PD-L1 inhibitors have recently been approved or are currently tested in larger confirmatory phase III studies. The licensing situation (FDA; USA) is shown in ▶ **Fig. 1**. Already, there have thus been over 5 years of clinical experience with this substance class. Combinations with antibodies against CTLA4 are also licensed for other tumour types. Moreover, substances against LAG-3 and B7-H3 are at the early clinical trial stage. With regard to breast cancer, only atezolizumab is so far licensed in combination with nab-paclitaxel in TNBC patients whose immune cells in the tumour show PD-L1 expression [4].

Immunohistochemical testing for PD-L1 positivity

Some of the indications for PD-1/PD-L1 antibodies are linked with a diagnostic test for PD-L1 in the tumour tissue, and various immunohistochemical methods and algorithms are used. While some consider the expression only in immune cells in the tumour [1], others assess the combined expression in immune cells in the tumour and also in tumour cells [2]. The IC (immune cell) score was used in the Impassion130 study with atezolizumab and the CPS (combined positive score) was used in the KEYNOTE-119, -355 and -522 studies with pembrolizumab. ▶ **Fig. 2** shows a definition of the two assessment methods and ▶ **Fig. 3** shows an example of CPS. There is little experience comparing different antibodies and determination methods. Such a comparison with the antibodies SP142 (IC ≥ 1 %), SP263 (IC ≥ 1 %) and 22C3 (CPS ≥ 1)



▶ **Fig. 1** Approval status (FDA, USA, status quo June 2019) of selected therapeutic PD-1/PD-L1 antibodies relevant for breast cancer (IA: initial approval [FDA, USA], IHC: immunohistochemistry, NSCLC: non-small cell lung cancer, MSI: microsatellite instability, HCC: hepatocellular carcinoma, PMBCL: primary mediastinal large B cell lymphoma, SCLC: small cell lung cancer, TNBC: triple negative breast cancer, RCC: renal cell cancer, * Tumour for which initial approval was granted, ** indication linked to PD-L1-testing). For all indications only the cancer entity is mentioned. Other criteria are not mentioned (e.g. therapy line or other diesease conditions). For exact information please refer to the official prescribing informations.

- Immune cell score (IC score)
- Cut-off in TNBC (atezolizumab): ≥ 1 %

$$IC = \frac{\text{Intratumour area with positive MIC}}{\text{Tumour area}} \times 100$$

- Combined positive score (CPS score)
- Cut-off reported in pembrolizumab studies: ≥ 1 %/≥ 10 %/≥ 20 %

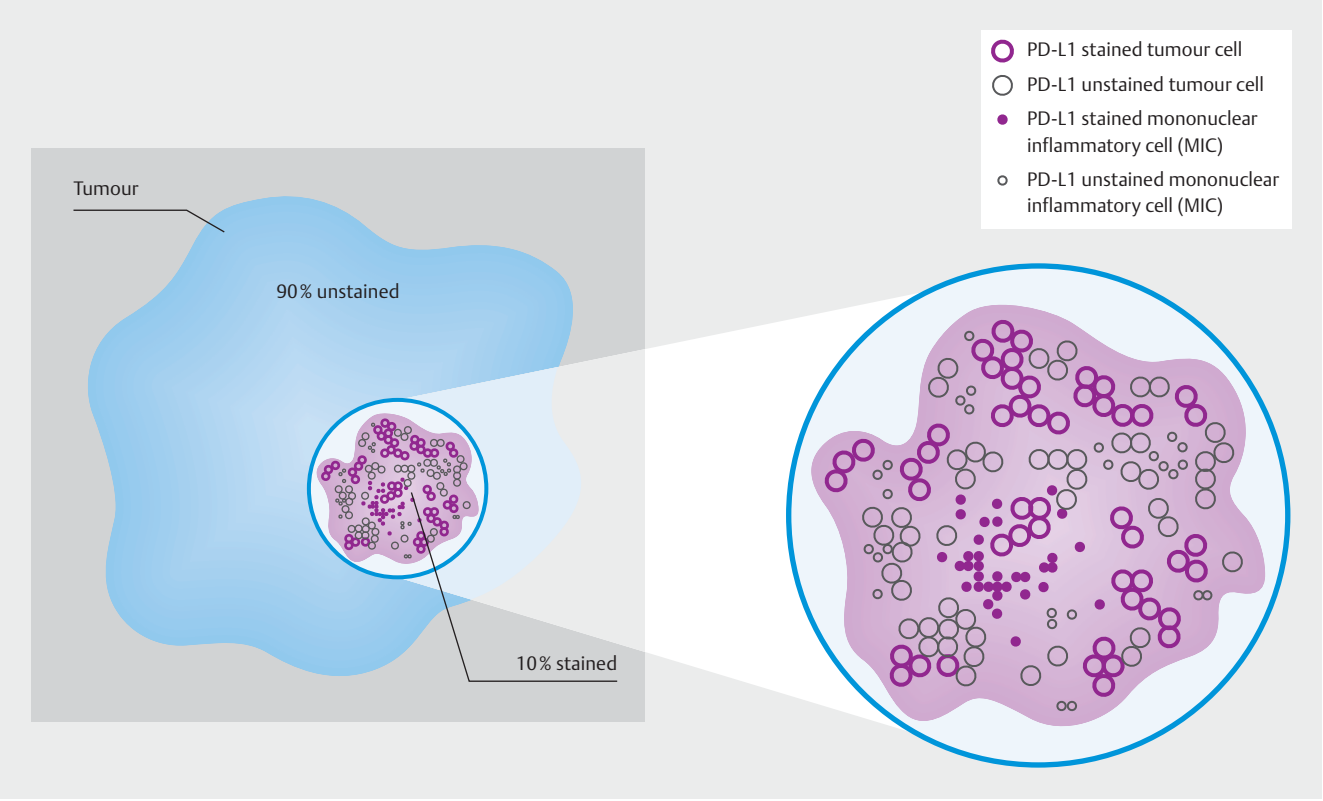
$$CPS = \frac{\text{Number of positive MIC + number of positive tumour cells}}{\text{Number of tumour cells}} \times 100$$

▶ **Fig. 2** Definitions of PD-L1 stains that were used for clinical approval studies [1, 2] (MIC: mononuclear inflammatory cells).

was carried out recently in the Impassion130 study [3]. All test methods were able to identify populations in which atezolizumab and nab-paclitaxel were more effective with regard to overall survival than monotherapy with nab-paclitaxel (*SP142* HR: 0.74; 95 % CI: 0.54–1.01/*22C3* HR: 0.78; 95 % CI: 0.62–0.99/*SP263* HR: 0.75; 95 % CI: 0.59–0.96) [3].

KEYNOTE-119

With regard to the treatment of TNBC patients in the first line setting with atezolizumab and nab-paclitaxel, it has already been shown that PD-L1 positivity with the IC score is necessary for efficacy, while no benefit was shown for atezolizumab in tumours with a negative IC score [4]. Knowledge of these data and experience with other diseases raise the questions of



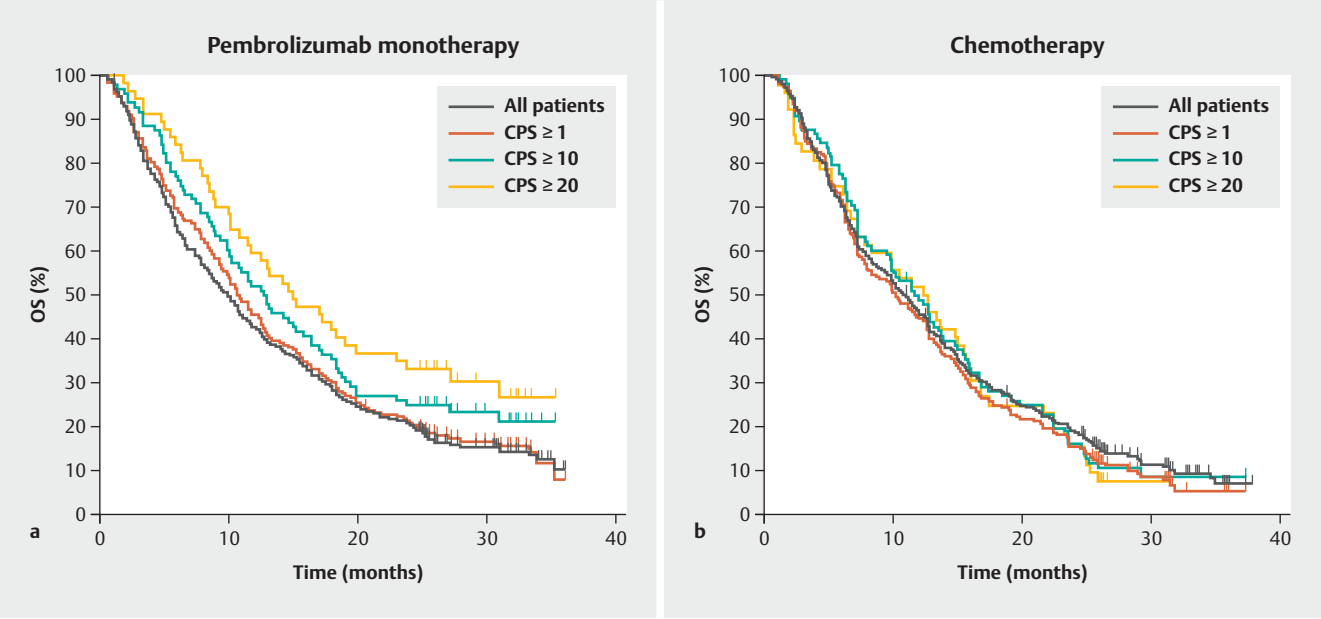
▶ **Fig. 3** Example of CPS (combined positive score) assessment. There are approximately 100 tumour cells in the area which is stained for PD-L1. In this area there are approximately 80 stained cells (tumour cells and mononuclear cells). There are therefore approximately 8% positive cells in the entire tumour, which corresponds to a CPS of 8 (example taken from: [2]) (© Agilent Technologies, Inc. Reproduced with Permission, Courtesy of Agilent Technologies, Inc.). [rerif]

1. the efficacy of other PD-1/PD-L1 antibodies,
2. the efficacy of monotherapy,
3. other combination partners and
4. their effectiveness in later treatment lines.

In this context, the KEYNOTE-119 study shows important results. Patients with advanced triple-negative breast cancer who had already concluded at least one treatment line in the metastatic situation took part in this study. Following randomisation, the patients were treated either with monotherapy with the anti-PD-1 antibody pembrolizumab or chemotherapy (physician's choice: capecitabine, vinorelbine, eribulin or gemcitabine). Treatment did not depend on PD-L1 expression, but the CPS score was a stratification factor. The primary study aims were differences in overall survival in patients with a CPS score ≥ 10, a CPS score > 0 and, if these study aims were reached, in the overall group also. Overall, the study was negative, but a clear trend could be seen that pembrolizumab was superior to chemotherapy with increasing PD-L1 expression. The hazard ratios are given in ▶ **Table 1** and the overall survival with pembrolizumab or chemotherapy depending on the CPS score is shown in ▶ **Fig. 4**. It remains to be discussed whether PD-L1 expression in highly pre-treated patients can be used as a selection criterion for therapy with pembrolizumab. In view of the lack of standard therapies in advanced therapy lines, this could be an option.

KEYNOTE-522

Since anti-PD-L1/PD-1 therapies have become established for patients with advanced breast cancer, it makes sense to test this treatment in patients with early breast cancer also. Tumours in the treatment-naive situation should theoretically have a lower chance of developing an immune escape phenomenon because of the lack of therapeutic exposure. A certain superior efficacy in the neoadjuvant treatment situation was already shown in the Gepar-Nuevo study, although the study result was not statistically significant [5]. In the KEYNOTE-522 study, the addition of a checkpoint inhibitor has now been evaluated in a large neoadjuvant phase III study [6]. Patients with a triple-negative tumour were included in this study if neoadjuvant chemotherapy was indicated. The patients were treated with platinum-containing chemotherapy or platinum-containing chemotherapy with the addition of pembrolizumab. The patients were not preselected according to criteria that consider the expression of PD-1 or PD-L1. A total of 1174 patients were randomised in a 2:1 ratio. It was shown that the pathological complete remission rate (pCR rate) was increased from 51.2 to 64.8% by the addition of pembrolizumab [6]. This difference was statistically significant ($p = 0.00055$). Interestingly, the effect was not dependent on the CPS score. In patients without PD-L1 expression, pCR was shown in 30.3% of cases with chemotherapy, while pCR was seen in 45.3% of cases with chemotherapy and pembrolizumab. With a CPS ≥ 1 the pCR rates



▶ **Fig. 4** Overall survival according to CPS score in the KEYNOTE-119 study separately for patients treated with pembrolizumab (**a**) and patients treated with chemotherapy (**b**). (modified from [45]).

▶ **Table 1** Comparison of overall survival between pembrolizumab and chemotherapy in the KEYNOTE-119 study according to CPS subgroups (from [45]).

CPS score	Number of patients Pembro vs. chemo	median OS Pembro	median OS Chemo	HR (95% CI)
Total ITT population	312 vs. 310	9.9 (8.3–11.4)	10.8 (9.1–12.6)	0.97 (0.92–1.15)
CPS ≥ 1	203 vs. 202	10.7 (9.3–12.5)	10.2 (7.9–12.6)	0.86 (0.69–1.06)
CPS ≥ 10	96 vs. 98	12.7 (9.9–16.3)	11.6 (8.3–13.7)	0.78 (0.57–1.06)
CPS ≥ 20	57 vs. 52	14.9 (10.7–19.8)	12.5 (7.3–15.4)	0.58 (0.38–0.88)

were 54.9% (chemotherapy) and 68.9% (chemotherapy + pembrolizumab).

With regard to event-free survival (EFS), patients on pembrolizumab had a lower risk for a disease event (HR = 0.63; 95% CI: 0.43–0.93) [6]. However, statistical significance was not reached formally for this interim analysis. The follow-up for this analysis was extremely short and few events occurred. Future interim analyses must therefore be awaited.

Hormone Resistance

Update on CDK4/6 inhibitors – growing data on overall survival

Combined treatments that aim to overcome mechanisms of primary or secondary endocrine resistance have been investigated for a few years. Everolimus was one of the first substances that showed a marked benefit with regard to progression-free survival [7] but which did not extend to overall survival [8]. The CDK4/6 inhibitors (CDK4/6i), in combination with anti-endocrine therapy, uniformly showed an improvement in progression-free survival with hazard ratios between 0.5 and 0.6 (summarised in [9]). Some of these studies have already been analysed with regard to overall survival. ▶ **Table 2** gives an overview of PFS and OS data.

With regard to overall survival also, similarity can be identified between the studies. As with all substance classes in which no direct comparison has been made between the substances, it is difficult to draw conclusions on whether one or the other substance has greater effectiveness. It is also difficult to assess minor differences with regard to the side effect profile. Three studies to date have shown a statistically significant survival advantage (MONALEESA-3, MONALEESA-7, MONARCH-2) [10–12], while this aim was shown only with a p value of 0.09 in the PALOMA-3 study, which showed however a a similar effect size [13]. The results of the MONARCH-3, PALOMA-2 and MONALEESA-2 studies are still pending and will surely be able to provide additional information about this substance class.

While it has now been shown that overall survival is better with combined therapy consisting of CDK4/6i+ET than with monotherapy, the question of whether this is a long-term effect has not yet

▶ **Table 2** Progression-free survival and overall survival for the reported phase III studies with a CDK4/6 inhibitor (date of PFS and OS: month the database closed for the first analysis).

Study	n	Recruitment	PFS date	OS date	PFS (95% CI)	OS (95% CI)	Reference
PALOMA-3	521	10/2013–08/2014	12/2014	04/2018	0.42 (0.32–0.56)	0.81 (0.64–1.03)	[13,46]
MONALEESA-7	672	12/2014–08/2018	08/2017	11/2018	0.55 (0.44–0.69)	0.71 (0.54–0.95)	[12,47]
MONALEESA-3	726	06/2015–06/2016	11/2017	06/2016	0.59 (0.48–0.73)	0.72 (0.57–0.92)	[11,48]
MONARCH-2	669	08/2014–12/2015	02/2017	06/2019	0.55 (0.45–0.68)	0.76 (0.61–0.95)	[10,49]

PFS: progression-free survival, OS: overall survival, CI: confidence interval

been answered. At the present time, it can only be concluded that fewer deaths occurred during the (short) follow-up period of the reported study in the stated circumstances.

Biomarkers and CDK4/6 inhibitors

Data that analysed mutation frequencies before the start of treatment and at the time of progression have already been published in the PALOMA-3 study. This showed that a *PIK3CA* mutation, which was not detectable at the start of treatment, was found in 8.2% of patients at the end of treatment [14]. This is important especially because it was shown in the SOLAR-1 study that combination with the PIK3CA inhibitor alpelisib and fulvestrant achieved improved progression-free survival in patients with a *PIK3CA* mutation compared with treatment with fulvestrant alone [15]. A small subgroup analysis suggests that this effect is independent of prior treatment with a CDK4/6 inhibitor [15]. Large studies of treatment with alpelisib after a CDK4/6 inhibitor are still recruiting and will deliver extensive data on the efficacy of alpelisib after CDK4/6 inhibitor therapy (BYLIEVE study).

The data on *PIK3CA* mutation accumulation from the PALOMA-3 study show that planning of therapy sequences in future may be linked to targeted molecular diagnostics. In another small study of letrozole and ribociclib (n = 5) with paired tumour samples before treatment and on progression on therapy, it was shown that the loss of expression can also have a role through a loss of gene copies [16]. Four of these 5 patients had a loss of RB or PTEN [16]. Even with the small number of patients, these results are interesting because they were supported by preclinical experiments and it was already implied that a loss of PTEN could be associated with resistance to PI3K inhibitor therapy [17]. PTEN loss is of particular interest in the context of new treatments because the tumour suppressor PTEN is a counter-regulator of the Akt/PI3K signalling pathway and loss suggests lack of counter-regulation of this signalling pathway.

The interaction between PIK3 and PTEN appears, however, to be more complex in that the different subunits of PIK3 play a different role in PTEN-deficient breast cancer [18]. Future studies will clarify whether PI3K inhibitor therapy has a part to play in such patients.

It should be noted that loss of gene copies of RB and/or PTEN was also investigated in the PALOMA-3 study but was not found there [14].

PARP Inhibition

Another treatment that was introduced based on a biomarker is treatment with a PARP inhibitor. An improvement in PFS was shown in large phase III studies for patients with HER2-negative, advanced breast cancer and a germline mutation in *BRCA1* or *BRCA2* (OlympiAD study and EMBRACA study) for the two PARP inhibitors olaparib and talazoparib compared with chemotherapy [19, 20]. Patients on olaparib, who had not received any chemotherapy for their metastatic disease, even showed an overall survival advantage. It was also shown that monotherapy with the targeted PARP inhibitor leads to an improvement in quality of life compared with chemotherapy [21, 22].

PARP inhibitors in combination with platinum in patients with breast cancer and BRCA1/2 mutation

While the OlympiAD and EMBRACA studies compared a PARP inhibitor and non-platinum-containing mono-chemotherapy, the question arises in patients with a germline mutation in *BRCA1* or *BRCA2* of whether platinum-containing chemotherapy can achieve similar effects. It is known that a BRCA1/2 mutation is a predictor for the particular efficacy of platinum therapy. The TNT study showed this in a comparison with therapy with a taxane [23]. The high efficacy of platinum chemotherapy in patients with a BRCA1/2 mutation was also shown in the neoadjuvant studies [24–26]. Consequently, the question is whether PARP inhibitor therapy plays a part in patients with a BRCA1/2 mutation in addition to or compared with treatment with platinum-containing chemotherapy. In the neoadjuvant situation, it has already been shown in the GeparOLA study, conducted in patients with a *BRCA1/2* mutation (germline or somatic) or confirmed homologous recombination deficiency (HRD), that olaparib/taxane followed by anthracycline-containing chemotherapy leads to a similar or slightly improved nominal pCR rate compared with carboplatin/taxane followed by the anthracycline-containing chemotherapy [27]. In the recently presented BROCADE-3 study, this topic was investigated with the PARP inhibitor veliparib in the metastatic treatment situation [28]. This study included patients with advanced HER2-negative breast cancer who had a germline mutation in *BRCA1/2*, had not received more than 2 chemotherapies in the advanced situation and had received a maximum of one treatment line with platinum-containing chemotherapy, after which no rapid progress (≤ 12 months) was permitted. 513 patients in total were included in the study, randomised 2 : 1 in fa-

vour of the PARP inhibitors; one arm received veliparib + carboplatin + paclitaxel and the other arm was given only carboplatin + paclitaxel. With regard to the primary endpoint of PFS, a statistically significant benefit was reported with a HR of 0.70 (95% CI: 0.57–0.88) [28]. This effect did not extend to overall survival in the early analysis [28]. With regard to side effects, more grade 3–4 thrombopenia (40 vs. 28%) and more anaemia (all grades, 80 vs. 70%) was seen with veliparib + chemotherapy. The other side effects were similar between the two groups, with a slightly higher general side effect rate in the veliparib arm [28]. Comparable data are not available for the other PARP inhibitors although prior therapy with platinum-containing chemotherapy was permitted in the studies of olaparib and talazoparib, as in the BROCADE-3 study [19, 20].

PARP inhibitors in the primary treatment of ovarian cancer

In ovarian cancer, clear benefits were shown in three recently reported studies for patients who were treated with a PARP inhibitor as maintenance therapy after primary diagnosis.

Patients with high-grade ovarian cancer/fallopian tube cancer/peritoneal cancer stage III or IV were enrolled in the PAOLA-1 study and treated either with bevacizumab as maintenance monotherapy or with a combination of olaparib and bevacizumab after platinum- and taxane-containing chemotherapy. The study showed a benefit overall for the combined arm with a HR of 0.59 (95% CI: 0.49–0.72). The effect appeared to be much more prominent in the group of patients with a *BRCA* mutation (HR = 0.31; 95% CI: 0.20–0.47) than in patients without *BRCA* mutation (HR = 0.71; 95% CI: 0.58–0.88) [29]. It was already suspected for breast cancer that a *BRCA* mutation interacts with angiogenesis: in the GeparQuinto study, a pCR rate of 61.5% was achieved in neoadjuvant treatment with a combination of chemotherapy and bevacizumab [30].

The PRIMA study, in which treatment with niraparib was compared with placebo after the initial chemotherapy, investigated a similar question to the PAOLA-1 study. Here, too, a benefit in the overall population in favour of the PARP inhibitor was demonstrated with a HR of 0.62 (95% CI: 0.5–0.76). In the PRIMA study, too, this effect was more apparent in patients with a homologous recombination defect (HRD) based on a *BRCA1/2* mutation (HR = 0.40, 95% CI: 0.27–0.62), while the HR was 0.50 (95% CI: 0.31–0.83) in patients with the HRD without BRCA1/2 mutation. In patients without the HR defect, the HR was 0.68 (95% CI: 0.49–0.94) [31].

The VELIA study, was also conducted with veliparib in the primary treatment of ovarian cancer [32]. In this three-arm study, as in PRIMA, no maintenance treatment with bevacizumab was given. However, the PARP inhibitor was combined with chemotherapy. The patients therefore received either chemotherapy with carboplatin and paclitaxel or this chemotherapy with veliparib or, in the third arm, the combination of chemotherapy + veliparib, followed by maintenance therapy with veliparib. The veliparib arm without maintenance therapy did not show any improvement compared with the chemotherapy arm, while the veliparib arm with subsequent veliparib maintenance therapy showed a benefit in the overall population with a HR of 0.68 (95% CI: 0.56–0.83). In this study, too, the effect was more obvious in the group of patients who had a mutation in *BRCA1* or *BRCA2* (HR = 0.44; 95% CI: 0.28–0.68) [32].

Overall, it can be confirmed that PARP inhibitor therapy represents clear progress for patients with ovarian cancer and will rapidly become part of clinical practice.

Biosimilars

Is trastuzumab the same as trastuzumab?

Development of a range of biosimilars became possible with the expiry of the patent for the reference trastuzumab. Because of the biological production process, biosimilars are not completely identical to the reference product but the approval process requires that the quality of the product is comparable to that of the reference product, and likewise the efficacy and side effects. In the comparative studies, however, major differences between the reference trastuzumab and the biosimilar were noted in a few of these studies (summarised in [33]). In the case of SB3, this appeared to be the consequence of a reduced efficacy of the reference trastuzumab.

In the neoadjuvant study, treatment with the reference trastuzumab and chemotherapy was compared with treatment with chemotherapy and the SB3 trastuzumab in HER2-positive patients. The pCR rate with SB3 that was nearly 10% higher than with the reference trastuzumab [34, 35]. Differences were also found in recurrence-free survival and overall survival. Events in the form of recurrence (HR = 0.47; 95% CI: 0.26–0.87) and overall survival (HR = 0.37; 95% CI: 0.13–1.04) occurred markedly more seldom in the SB3 treatment arm [36].

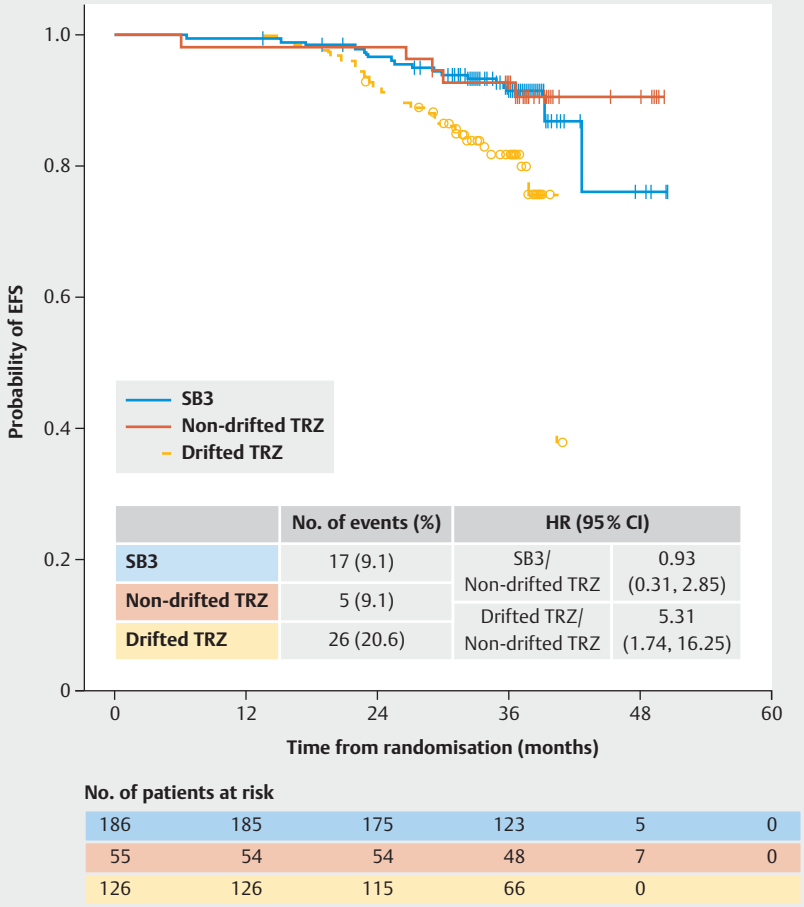
In investigations regarding antibody-dependent cellular cytotoxicity (ADCC), which plays a part in the antibody-mediated action of the natural killer cells on the tumour cells, it was found that certain production lots of the reference trastuzumab appeared to suggest reduced ADCC activity (relative ADCC activity, relative FcγRIIIa binding activity) [37].

When the study was analysed separately according to the groups SB3, reference trastuzumab with normal ADCC characteristics and reference trastuzumab with compromised ADCC characteristics, it was seen that only the group with the reference trastuzumab and compromised ADCC showed clinically visible poorer prognosis with an over five-fold increased risk for recurrence compared with the non-compromised reference trastuzumab (HR = 5.31; 95% CI: 1.74–16.25) [36]. ▶ **Fig. 5** shows the corresponding Kaplan-Meier curves.

These data show that large differences in efficacy, hitherto apparently unidentified, can occur in the production of monoclonal antibodies, which are very probably of clinical relevance.

Big Data and Digitisation of Medicine

Technologies that investigate large amounts of data with machine learning or deep learning methods are being used and implemented ever increasingly in medicine [38]. Applications, some of which are already under development, could thus have a direct influence on clinical practice in the near future.



▶ **Fig. 5** Kaplan-Meier curves for the 3 groups in the SB3 biosimilar study NCT02771795, which represent the groups chemotherapy + SB3 trastuzumab, chemotherapy + reference trastuzumab without ADCC drift and chemotherapy + reference trastuzumab with ADCC drift (copied from [36] under the CC-BY-NC-ND open access licence).

Digital pathology and machine learning

One of the main fields of research is processing of digital image data, which can be important especially for radiological and histopathological images. In an article that appeared recently, an attempt was made to establish algorithms with machine learning that predict from the histopathological appearance whether a tumour has microsatellite instability (MSI).

Microsatellite instability is the result of defective mismatch repair mechanisms in DNA repair, which affects the mutation rate in the entire genome, but especially in short tandem repeats (microsatellites). MSI is usually determined by immunohistochemistry for the expression of the 4 mismatch repair genes MLH1, MSH2, MSH6 and PMS2 [39]. A loss of expression is generally found with a mutation. This condition is often found in colon cancer and endometrial cancer.

It was shown in a recently published article how this prediction can also be made with haematoxylin-eosin staining by means of deep learning [40]. The AUC in a validation cohort of 378 patients with colorectal carcinoma was 0.84. Such methods are also conceivable for other tumour types, such as ovarian cancer or cervical cancer.

Support of clinical decision-making

Another area of research is the implementation of decision-making algorithms in routine clinical practice or tumour boards. Clinical decision-making could benefit in many ways from a big data or machine learning approach. On the one hand, systematic analysis of patient data including treatment data and outcome data (prognosis and quality of life) offers a large opportunity for using the data recorded in routine clinical practice for modern machine learning analysis and so make suggestions that will result in better quality of life or prognosis for the individual patient. On the other hand, decision-making could be improved by avoiding error. Errors can occur both in the interpretation of findings and in the compilation and presentation of findings, which lead to sub-optimal decisions. Digitisation and plausibility checking at this level could help to avoid decision errors [41]. In the PRAEGNANT network in Germany [42], machine learning methods, for example,

are used to try to optimise treatment decisions [43, 44]. Useful predictions of the optimal clinical procedure have already been achieved by means of encoding with recurrent neuronal networks and what is known as tensor decoding [43, 44].

The extent to which decision support before, during or after real decision-making can be integrated in routine clinical practice remains to be seen. Appropriate studies must be conducted that should integrate both doctors and patients.

Prospects

With the new treatments, atezolizumab, the PARP inhibitors in breast cancer and soon the PI3K inhibitor alpelisib also, new treatments have been introduced that are associated with a biomarker that predicts the efficacy of these therapies. Implementation of these tests will be just as demanding as extending the scientific understanding of these markers. For example, atezolizumab therapy in the metastatic situation is linked to PD-L1 positivity of the immune cells, while in the neoadjuvant setting, pembrolizumab increased pCR rates independent of PD-L1 expression. In the far advanced treatment situation, however, pembrolizumab efficacy appeared to correlate with PD-L1 expression.

These examples show that simultaneously with the introduction of new predictive molecular tests into routine clinical practice, assistance in interpreting and assessing the relevance of the test results must be provided to therapists.

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Conflict of Interest

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